affected were very young and showed absolutely no change in the vessel-walls, while in other cases, as in our own, though arterio-sclerosis was present in the vessel-wall in places, none was to be observed in the immediate neighborhood of the tubercle nodules. It is conceivable that in cases of this sort, in which large quantities of bacterial toxins are circulating in the blood-stream, these might be able to cause localized areas of lessened resistance in the vessel-wall and prepare it for the lodgement of the tubercle bacillus. That bacterial toxins, without the presence of the bacteria themselves and without accompanying traumatism, are well able to cause changes in the aorta is shown by the researches of Boinet and Romary,[1] who were able to produce definite lesions by the injection of the toxins of tetanus and of diphtheria. Direct infection from the lymph vessels is hardly to be thought of, the current being in the wrong direction to convey infection from the neighboring glands, and the vessels in all probability reaching only the same distance into the vessel-wall as do the bloodvessels—*i. e.*, to the middle of the media.

The possibility of these tubercle nodules being due to the invasion of small parietal thrombi by the tubercle bacillus must be thought of, as invasion of thrombi by tubercle bacilli has been observed in connection with heart lesions in some instances; but in none of the reported cases was there evidence to support this theory. In Stroebe's case there is distinct mention made of the fact that nothing like changed blood-pigment was present in the tubercle nodules, nor could we find any evidence of such in our cases. The presence of a small amount of fibrin in the tubercles, such as occurred in Stroebe's cases, is no evidence of thrombotic origin, for Falk[2] has shown that a fair percentage of tubercles contain fibrin at some stage in their development. The results of the experiments of Boinet and Romary on the production of aortic inflammatory lesions lead us to hope that in the future the origin of aortic tubercles may be made clearer by similar methods.

COMBINED TYPHOID AND MALARIAL INFECTION.

REPORT OF A CASE AND REVIEW OF THE LITERATURE, WITH SPECIAL REFERENCE TO THE SO-CALLED TYPHO-MALARIAL FEVER.

By Irving Phillips Lyon, M.D.,
BUFFALO,
FORMER HOUSE PHYSICIAN, JOHNS HOPKINS HOSPITAL, BALTIMORE.

For the past half-century there has been much controversy among medical men on the question of the coexistence of typhoid and malarial

[1] Boinet and Romary. Archives de Médecine Expérimentale, 1897, p. 902.

[2] Falk. Virchow's Archiv, Band cxxxix. S. 339.

infection in the same subject and the clinical picture resulting. The various theories that have been advanced on this subject are too many and diverse to enumerate. So long as the exact cause and nature of both diseases were unknown it is natural that little headway could have been made in solving the problem. To-day, however, with the cause and nature of each of these diseases established and resting on scientific demonstration, we should expect that the question of the coexistence of the two diseases would have been solved beyond controversy. This, however, is not the case, and almost as much uncertainty exists as formerly. Few of the cases clinically diagnosticated as combined typhoid and malarial infection, *typho-malarial* fever, etc., have been studied by modern laboratory methods of scientific research. It is clear, however, that until such exact methods of study shall be generally employed the subject of discussion will remain open.

It is my purpose in the present article to collect from the literature and present, in abstract, such cases of combined typhoid and malarial infection as have been studied by the best methods of modern investigation, and to draw from these cases evidence on the nature and general clinical picture of such combined infections. I shall pay special attention in this brief survey to the subject of the so-called *typho-malarial* fever. For the purpose of this study I have accepted such cases only as meet the following requirements:

1. That typhoid fever and malarial fever coexist in the same individual.

2. That this coexistence be shown (*a*) by the discovery of the parasites of malarial disease in the blood, and (*b*) by strong evidence, clinical, pathological, bacteriological, etc., of true typhoid fever.

I have been able to collect from the literature twenty-nine cases meeting these criteria, to which I shall add one case that has been under my care recently in the Johns Hopkins Hospital, in Dr. Osler's service. In all, then, I shall present brief notes of thirty cases of true combined typhoid and malarial infection. I shall refer, also, to other cases, presumably combined typhoid and malarial disease, described in the literature, but not meeting the above requirements.

The case that I have had under my observation and charge in the Johns Hopkins Hospital is as follows:

H. B., male, aged forty-eight years, a carpenter, entered Johns Hopkins Hospital, Baltimore, January 5, 1898, complaining of "chills and fever." Hospital No. 21,646.

While working at Hawkins Point, on Chesapeake Bay, a few miles from Baltimore, he had three successive attacks of "chills and fever," occurring respectively in June, August, and October, 1897. The chills were typical, severe, and shaking, lasting from one to two hours, and required him to stop work for about two weeks during each of the periods mentioned. He took quinine irregularly during each attack, not between the attacks. He lost thirty-five pounds in weight between his first attack of malarial fever, in June, and the beginning of his present illness, in December, and during this whole period felt weak and ill.

The first symptoms of his present illness date from December 18th, and from this date until his admission, on January 5th, he had daily chills, slight and confined to his back. Headache accompanied the chills, and sometimes backache and nausea. Vomiting occurred once, on December 19th. . There were no sweats, cough, nor epistaxis. The bowels were regular. Quinine was taken regularly three times daily. He took to bed January 2, 1898.

On admission, January 5th, his condition was as follows: Temperature, respiration, and pulse normal; tongue dry and coated; lungs negative except for a few crackles at the left base; a soft systolic bruit at the heart's apex; liver and spleen both enlarged and felt just below the costal margin, and tender on palpation; abdomen full and rather tense, but not tender; no gurgling in iliac fossæ; a few rose-spots on the abdomen; bowels constipated; Ehrlich's diazo-reaction in the urine; no malarial organisms in the blood; Widal's serum reaction not present.

During the forty-eight hours following admission two suspicious febrile paroxysms occurred without chills or sweating, but accompanied by headache. Repeated examinations of the blood for malarial parasites were negative. After the first forty-eight hours the temperature assumed a typical typhoid course, which was maintained throughout until convalescence. Quinine was not given, except as hereafter stated. The course of the typhoid fever was characteristic and of average severity. The bowels were constipated throughout. Numerous rose-spots appeared over the trunk, arms, and legs. The Widal serum reaction developed, and was positive. The leucocyte count was characteristic, falling to 4000. Blood cultures taken on several occasions proved negative, as also cultures from the feces, so far as the differentiation of the bacillus typhosus is concerned. The temperature reached normal on the thirty-first day of the disease (dating from the time the patient took to bed), and the patient entered upon convalescence.

After nine days of normal temperature a febrile paroxysm developed, without chill or sweating. A second similar paroxysm occurred two days later, and a third paroxysm two days after this. The blood was examined during the third paroxysm, and showed numerous full-grown pigmented tertian malarial organisms and a few young hyaline forms in the red blood-corpuscles. Extracellular pigmented forms and pigmented leucocytes in active amœboid movement were observed later in the day. On the following day a few full-grown organisms were observed, and a day later stray pigment granules in the serum. Quinine was given in large doses at the time of the first discovery of malarial organisms, and was continued until the patient's discharge. After the third paroxysm no further evidence of malarial fever was seen, and the patient was discharged, well, February 24th.

To summarize briefly: this case had successive attacks of malarial fever in June, August, and October of last year, imperfectly treated with quinine. Between these attacks, and following them, the patient lost weight, had little appetite, and was weak. The malarial infection was probably present throughout and dormant in the intervals. The repeated daily chills that occurred from December 18th to January 5th were probably, but not surely, malarial. It is possible that they were merely the initial chills[22] sometimes seen in typhoid. The febrile paroxysms seen on the patient's admission may possibly have been malarial in origin, though the negative results of repeated blood examinations make this very doubtful. At any rate, the malarial organisms showed no further influence on the course of the typhoid fever until convalescence had been well established. The course of the typhoid was typical and of at least average severity. Malarial paroxysms occurred during convalescence and yielded promptly to the action of quinine, and the patient quickly recovered. It is to be noted also that for eighteen days prior to admission the patient had taken quinine three times daily.

The cases furnished by the literature,* twenty-nine in number, are as follows:

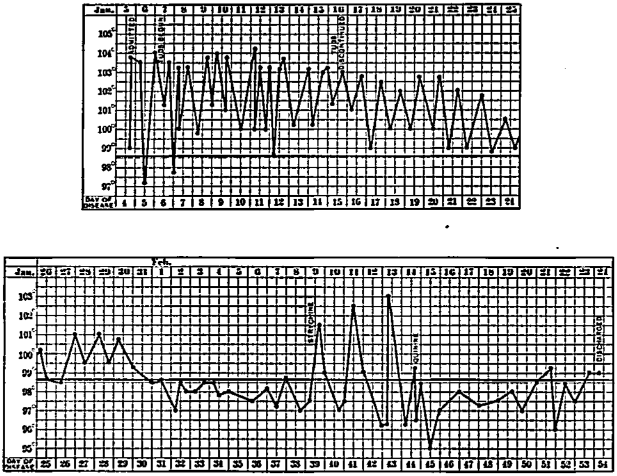
	Cases.	Mortality.	Per cent. mortality.
Osler	1	0	0.0
Da Costa	1	0	0.0
Kinyoun	5	2	40.0
Thompson	3	0	0.0
Laveran	2	0	0.0
Vincent	17	8	47.0
	29	10	34.4

Osler's [23] [24] case. The patient was admitted to the Johns Hopkins Hospital October 16, 1891. (Hospital No. 4051.) During the sixteen days prior to admission the patient had had headache and cough, occasional epistaxis, and three chills. On admission the temperature was 100° F., falling to 96° F. at midnight. "The blood on the 17th showed fairly numerous, non-pigmented, intracellular, hyaline bodies." Quinine was begun. At 12 M. on the 17th the temperature began to rise, and at 3.30 P.M. the patient had a chill, after which the temperature rose to 104.2° F., falling to normal at 12 M. on the 18th. During the next several days there were slight oscillations in the temperature, which remained nearly normal. "The last malarial organism seen in the blood was an ovoid body, with coarse pigment granules, which was seen on the 23d." The temperature began to rise on the 22d, reaching 104.8° F. at 4 P.M. on the 23d, the beginning of a long, severe attack of typhoid fever. Quinine was discontinued on the 26th. The course of the typhoid fever was typical, but of great severity, the temperature not falling to normal until between the fifth and sixth weeks. Rose-spots developed during the course. The patient had in all sixty-eight baths. No further evidence of malaria appeared, and the patient was discharged, well, on January 19th. (The temperature-chart is produced in full.)

---

* Anders'[25] cases are omitted from this enumeration, because no record in detail of the cases has been published. In a letter to the writer, however, Dr. Anders states that "tertian malarial organisms were noted in five" of the eight cases, and that "in two out of the five cases in which malarial micro-organisms were found, distinctive and conclusive evidences of typhoid fever were furnished by my notes, such as enlarged spleen, characteristic eruption, the characteristic temperature-curve, peculiar nervous symptoms, etc."

TEMPERATURE-CHART.



Admitted January 5th, on fourth day of disease. Tubs begun on January 7th, and discontinued January 16th. Strychnia sulph., gr. $^1/_{60}$, twice daily, begun February 9th and continued until discharge. Quinine sulph., gr. v t. i. d., begun February 14th and continued until discharge, on February 24th.

Da Costa's[38] case. Patient entered hospital November 9th. About three weeks before, patient began to have headache, backache, and paroxysms of chill, high fever, and sweating, occurring on alternate days. These paroxysms continued to occur for two weeks. The week before admission diarrhœa began and the fever became persistent, accompanied by slight cough, loss of flesh, and weakness.

After admission the patient had no chills, but had a "continued fever, which exhibited the features of typhoid." The temperature-curve for the first few days showed marked irregularity. On admission the temperature was 97° F., rising to 102° F. during the day, declining to 100° F. on the next morning, and again rising by evening to 103.8° F. On the day following the morning temperature was 100.6° F. and the evening temperature 103.2° F. After this the temperature showed less irregularity. The clinical picture was characteristic of typhoid, and a large number of rose-spots appeared. Convalescence became established, and recovery followed. The blood examination (at what time made, not stated) showed " marked brown pigmentation, and with these masses there were various forms of malarial organisms, though not the crescentic forms. The white corpuscles contained a great deal of pigment, irregular in shape; there was none in the red cells. On the whole, the evidence of malaria in the blood is striking and unquestioned."

(In a personal communication to the writer Dr. Da Costa states that the above description of the parasites is inaccurate, and that pigmented hyaline organisms were found in the red blood-corpuscles.) The temperature-chart of the case is published. Quinine was administered.

Kinyoun's[21] cases. Kinyoun studied the cases of malarial fever and typhoid fever at the New York Marine Hospital for the presence of malarial organisms in the blood and the bacillus of Eberth in the spleen and intestinal canal. More than one hundred cases of malaria were studied. The writer does not state the number of cases of typhoid fever seen. All of these cases were in sailors coming from the Southern States and from Virginia in particular. Among these he observed five instances of mixed typhoid and malarial infection. He divided his cases clinically into two groups, as follows:

Group I., including " cases in which the symptoms of malarial fever predominate, masking the enteric lesion," two cases.

Group II., including " cases in which the symptoms of enteric fever are most prominent," three cases.

In all cases the malarial organisms were found in the blood and Eberth's bacillus in the spleen or intestinal canal. The types of malarial organisms observed are not mentioned, and temperature-charts are not reproduced.

Case I.—Two days before admission patient had a chill, followed by fever marked by a remission; on day of admission chilly sensations, with a rise in temperature, followed by remission. The blood examination showed a large number of the " plasmodia malariæ, found both in the serum and within the blood-corpuscles." The epigastric region showed tenderness and the spleen was considerably enlarged. " On the fifth day after admission there appeared on his abdomen several suspicious-looking spots suggestive of enteric complications. On the day following he had slight epistaxis and a tendency to diarrhœa, tenderness in the right iliac fossa." At this time " a bacillus answering to the description of that described by Eberth was isolated from the stools," and the blood examination still showed "" the malarial parasites, in greatly diminished numbers, confined to the corpuscles." During the next week the entire symptoms became marked, the remissions in the fever ceased, and the temperature-curve was characteristic of typhoid fever.

Case II.—The symptoms were not so pronounced as in the first case, but, on the whole, the case did not differ from the first. " The plasmodium malariæ was found in the blood in abundance, and later the typhoid bacillus was isolated from the stools."

Group II., three cases. " The enteric symptoms were well marked, giving a clear history of the disease. The history gave the prodromal period, lassitude, etc., followed by diarrhœa, epistaxis, and tympanites, and in one case slight hemorrhage." The "malarial parasite" was found "confined to the corpuscle, not free in the blood serum." The typhoid bacillus was isolated in every case. In one case during the third week in convalescence, with normal temperature, a rise of temperature to 39° C. occurred, lasting four hours. Twenty-four hours later a similar rise of temperature occurred. The blood was examined and the "plasmodium" was found. Antiperiodic treatment was employed for a few days, and the case went on to speedy convalescence.

The two other cases of this group terminated fatally, one by peritonitis following perforation, and the other by pneumonia.*

Thompson's[25] cases. CASE I.—Patient denied having had ague; developed typhoid fever, which began typically, without any suggestion of malarial complication. Numerous rose-spots developed in successive crops. The disease pursued a prolonged course, with very severe and grave symptoms. On the thirteenth day a severe chill occurred, accompanied by a temperature of 106.6° F., without sweating. The blood examination showed malarial organisms "in exceptionally large numbers, invading the red blood-corpuscles and also independent of them." Quinine was administered. During the third week two similar paroxysms occurred, and quinine was again employed. No further manifestations of malaria appeared, and the case terminated with recovery. The temperature-chart is given.

CASE II.—Two weeks before admission patient had had five or six severe chills, accompanied by nausea, vomiting, slight diarrhœa, fever, and severe frontal headache. On admission unmistakable signs of typhoid fever were present, including many rose-spots on the chest, abdomen, and back. The urine showed the diazo-reaction. The disease ran a typical course of average severity. In all, thirty tubs were given. Defervescence became established on the thirty-first day. After seven days of normal temperature three quotidian paroxysms of chill, high fever, and profuse sweating occurred. Malarial organisms in abundance in the blood were found. Quinine was given. The patient showed no further evidence of malaria, and in a few days was discharged, cured. The temperature-chart is given.

CASE III.—Patient admitted on nineteenth day of illness, with all the signs of well-established typhoid fever. There was a distinct eruption of rose-spots on the abdomen and thorax. The course of the fever was of average severity, and the patient received in all twenty-one baths. Defervescence was established on the thirty-third day. After eight days of normal temperature two quotidian paroxysms of chill, high fever, and sweating occurred, and quinine was administered. The blood was not examined until twenty grains of quinine had been taken, and then showed no true malarial organisms, but "abundant malarial pigment granules were contained in the blood-cells." Recovery immediately followed. The temperature-chart is given.

(This case is included in our enumeration of cases on the evidence of the presence of malarial pigment contained in the blood-cells following the febrile paroxysms, despite the fact that living organisms were not found.*)

---

* A full report, presumably of this case, is published in the "Annual Report of the Supervising Surgeon-General of the Marine Hospital Service of the United States," Washington, 1890, p. 187.

Laveran's[15] [43] cases. CASE I.—Patient entered the hospital at Constantine, Algeria, August 2, 1882. Diagnosis on admission, typhoid fever. In March, 1881, patient had had a fever lasting three days, with herpes labialis. The fever disappeared without the use of quinine.

July 31, 1882. First symptoms of present illness; general malaise, general weakness, headache, burning thirst, and fever with chill. Fever persisted without marked remission until patient entered hospital, and continued also after admission, without remission. Typical symptoms of typhoid fever developed, but rose-spots never appeared.

August 11th. Fever began to subside.

20th. Defervescence complete and convalescence begun. The temperature had been typical of typhoid.

29th. Patient complained of chill, and said that for several days he had had a chill in the evening; evening temperature 39.5° C.

30th. At 8 A.M. the blood examination showed various forms of malarial parasites in large numbers; temperature about normal; quinine was begun; evening temperature 38.5° C.

31st. Apyrexia; parasites in the blood in reduced numbers; quinine continued.

September 5th. There has been no further evidence of malaria; patient discharged, well.

(The temperature-chart is not given.)

CASE II.—Patient entered the hospital at Constantine, Algeria, January 25, 1883, complaining of intermittent fever. Patient had been in the hospital at Philippeville in August, 1882, for twenty-three days, with intermittent fever; no return of fever until January 20, 1883.

January 20th to *24th.* Quotidian paroxysms of fever with initial chill regularly at 2 A.M.

24th. Morning temperature, 40.2° C.; evening temperature, 38.9° C.; anæmia well marked, earthy hue of face, mucous membranes pale, general thinness and feebleness, anorexia, tongue fair; blood examination showed malarial parasites and pigmented leucocytes; quinine begun.

25th. Morning temperature, 38.2° C.; evening temperature, 38.4° C.; anorexia.

25th. Apyrexia.

27th. Apyrexia; no organisms in the blood.

February 4th. Quinine discontinued.

8th. Patient complains of not sleeping, and general malaise and headache for the past few days; no chills; morning temperature, 39.5° C.; evening temperature, 40.6° C.; blood examination negative; quinine begun.

9th. Morning temperature, 39.7° C.; evening temperature, 39.9° C.; general symptoms of typhoid fever.

10th. Morning temperature, 39.6° C.; evening temperature, 40.1 C.; typhoid state pronounced.

---

* In a letter to the writer dated February 22, 1893, Dr. Thompson states that he has notes of several other cases of double typhoid and malarial infection that have recently occurred in New York, and that he has heard of the occurrence in New York of several cases more.

11th. Morning temperature, 39.3° C.; evening temperature, 40.3° C.; rose-spots on abdomen; quinine discontinued.

15th. Defervescence begun.

18th. Blood examination negative.

20th. Defervescence complete—*i. e.*, on the seventeenth day of the typhoid fever; apyrexia persisted until

March 8th. Chill; temperature, 40.3° C.; blood examination showed malarial parasites.

9th. Apyrexia; quinine begun.

14th. Apyrexia has persisted; no further evidence of malaria; quinine discontinued.

15th. Patient discharged, cured.

(Temperature-chart not given.)

(Laveran describes several other cases[16] [43] that were undoubtedly combined malaria and typhoid, as shown at autopsy, but they cannot be accepted in this enumeration, as they either occurred before the discovery of the malarial parasite or there is no note of the presence of the parasite in the blood.)

Vincent's[33] cases. Vincent, a French army surgeon, at the bacteriological laboratory of the Hospital du Dey, in Algeria, encountered seventeen cases of combined typhoid and malarial infection, which he called "fièvre typho-palustre." Sixteen of these cases were in soldiers from Madagascar and one in a soldier who contracted the disease in Algeria.

The clinical symptoms of the disease varied considerably between those of typhoid and those of malaria, but in a majority of the cases the symptoms of typhoid dominated the picture.

The first manifestations of the infection consisted in an initial rise of temperature, almost always rapid, sometimes abrupt, resembling malaria, with or without a chill, severe headache, general body pains, and sometimes epistaxis. Once established, the fever persisted, often irregular and capricious in its course, or higher in the morning than in the evening. Sometimes the initial fever was only transitory, and was followed by an almost normal temperature during the course of the disease, interrupted by an occasional high rise. The latter type was observed twice.

The pulse-rate followed the oscillations of temperature, remaining high in the intervals. It not rarely varied between 130 and 150, or more, to the minute. It was dicrotic, compressible, sometimes very small, and was accompanied by cardiac irregularities, etc.

Profound stupor, delirium, excitement alternating with depression, earthy hue of face, dusky, dry lips, teeth, and tongue, intense albuminuria were seen in all the cases, indicating the gravity of the infection. Death, following severe symptoms, occurred in some cases in the first week.

Thoracic complications (bronchitis and lobular pneumonia) were almost constant. Rose-spots were present in twelve of the seventeen cases. The right iliac fossa was tender on pressure. Constipation sometimes occurred, generally, however, diarrhœa, yellow and of fetid odor. In one case death followed choleriform symptoms. Two cardinal symptoms were always present: the earthy hue of the face and the enlargement of the spleen. Tenderness over the liver was also present. Death was often due to complications, such as myocarditis, parenchymatous nephritis, gangrene of the lung, lobar pneumonia, abscess of the kidney and the spleen, peritonitis, etc.

The convalescence was slow, establishing itself at the end of the third or fourth week, and often, during this period, isolated febrile paroxysms occurred. All cases were given large doses of quinine.

Pathological. In all cases the blood was examined during life and to the end of the infection, and malarial parasites (amœbæ, segmenting forms, and crescents) were found, except in one case in which, at autopsy, the parasites were found abundantly in the spleen.

Eight of the seventeen cases terminated fatally. In all the fatal cases, at autopsy, tumefaction and ulceration of Peyer's patches in varying degrees were noted. These lesions were often very small. The mesenteric glands were hypertrophied. The spleen was always enlarged, in one case weighing nine hundred grammes, and the surface had the color of graphite. The liver was hypertrophied, soft, and brown in color. The kidneys showed the characteristic lesions of parenchymatous nephritis. Microscopic examination of the liver and spleen showed melanosis. Sections of the spleen showed a number, sometimes considerable, of the organisms of malaria, especially the crescents. Cultures from the spleen were carefully studied and showed a bacillus presenting the morphological and biological characteristics of the *bacillus typhosus* of Eberth.

Vincent concluded, "from the anatomico-pathological changes which are found in the fièvre typho-palustre, and especially from the result of bacteriological and microscopical examinations of the blood and viscera, we believe that we may conclude that the syndrome studied is no other than a mixed infection due to the association of the bacillus typhosus and the pathogenic agent of paludism."

A separate narration of cases is not given, but four temperature-charts are given, showing as follows:

1. Abrupt rise of temperature from 36.1° C. on the first day to 40° C. on the second, falling to 39.1° on the third day, with death on the fourth day.

2. Temperature-curve most irregular, with three tertian paroxysms during the course, followed by death.

3. Temperature-tracing in general close to normal, with acute paroxysms occurring on the second, third, twelfth, and thirty-second days of the disease, with death on the thirty-ninth day.

4. Quotidian paroxysms of temperature on the fifth, sixth, seventh, eighth, and ninth days, with death on the tenth day.

Having now passed in review these thirty cases of combined typhoid and malarial infection, we shall attempt to derive from them what information they afford on the subject of the so-called *typho-malarial* fever.

The existence of mixed forms of intermittent and typhoid fever has been noted at various times by many writers. In 1781 Burserius[1] described them under the group-name "the proportionata." Hermann Schmidt[2] in 1830 described them, and divided them into two groups, viz., (1) "typhus intermittens subintrans," in which the typhoid element predominated, and (2) "febris intermittens typhosa," in which the intermittent fever was predominant. In Italy, Maillot[3] described them in 1836, and Felix Jacquot[4] in 1851. In the United States, Drake[5] observed the double infections before 1854, and designated them "remitto-typhous." Dickson[6] referred to them in 1855, and Levick[9] in 1863 gave them the name "miasmatic-typhoid fever." Many other references[11 13 15] to these mixed infections are found in the literature of different countries.

The term *typho-malarial* fever was introduced in the United States in 1862 by Woodward,[7 8 10 17] a surgeon in the army, who encountered in his service in the field during the war cases of fever which presented a clinical picture typical neither of typhoid fever nor of malarial fever, but apparently a compound of both. This fever he called *typho-malarial*, and on his suggestion this term was introduced by the Board of Medical Officers[17] in the blank forms of the monthly sick-reports of the army. As a result of the introduction of the new term in the army there were reported to the office of the Surgeon-General[14] during the war 57,400 cases of this disease, with 5360 deaths.

The new disease-name was quickly adopted and became general in the United States, and found its way into local health-board reports and eventually into many of the standard text-books of medicine, such as Flint, Loomis, Clymer, etc. It met with strong opposition,[12 16] however, in many quarters. Among French writers the disease was called by various terms, such as "fièvre typho-malarienne," "fièvre typho-malariale," "fièvre typho-palustre," "fièvre typho-paludéenne," "fièvre proportionnée typhoïdique," etc.

In 1876, at the meeting of the International Medical Congress in Philadelphia, Woodward[17] read a paper on the nature of "typho-malarial" fever, and, at this time, took the ground that it was a *hybrid* disease produced by the concurrent action of malarial and typhoid infection, and, on his motion, the following definition was adopted as expressing the opinion of the Section on Medicine: "Typho-malarial fever is not a specific or distinct type of disease, but the term may be conveniently applied to the compound forms of fever which result from the combined influence of the causes of the malarious fevers and of typhoid fever." This definition of "typho-malarial" fever is the one most generally accepted to-day by the advocates of the existence and prevalence of such a disease. But it is not to be understood that all physicians using this term have any such exact idea of its nature as is indicated by the above definition. The term "typho-malarial" fever, as Woodward pathetically remarked, has been used extensively by many physicians to denote any obscure febrile affection which offered diagnostic difficulty. The term is very widely employed in the Southern States, and is very common in the North as well.

Accepting, then, this definition of "typho-malarial" fever, what is the clinical picture of the disease? Its advocates[25] in America, as a rule, state that it is a prolonged fever, exhibiting typhoid characteristics, and ushered in and often accompanied during its course by repeated paroxysms of chill, high fever, and sweating. The onset of the disease is more abrŭpt than that of simple typhoid fever, and its termination is often by crisis. Bilious symptoms are frequent. Jaundice, or an icteroid hue of the skin, is more common. Abdominal tenderness, distention, etc., are usually present, though often slight. Diarrhœa may or may not be present. Rose-spots seldom develop. The course* of the fever is shorter and markedly milder than that of typhoid fever. The prognosis is consequently highly favorable and the mortality very low. Severe symptoms, such as hemorrhage, perforation, etc., sometimes, though rarely, occur, as in simple typhoid fever. As to the value of quinine, much diversity of opinion is found. All agree that it does not influence the course of the typhoid element, and many state that its influence in controlling the malarial manifestations is slight or entirely wanting. Others state that it is of distinct value in combating the malarial element.

The above clinical description of "typho-malarial" fever appears to be that given by a majority of its historians in America, though every conceivable addition to or subtraction from this symptomatology is found in the literature.

It must be noted, however, that the French descriptions of the disease differ in important respects from the American. Most of the French writers state that the course of the disease is usually severe and the mortality high;[13 18 19 20 24 33 43] that complications are common;[20 24 33] that rose-spots usually appear,[18,19,20,24,33,43] and that quinine has a modifying influence on the disease.[18,19,20,33,43] The French writers also hold various views as to the resulting clinical picture, some stating that the two diseases are simply superimposed the one upon the other, each preserving its individuality,[19,43] and others finding that the clinical picture varies markedly in individual cases,[44] in some showing a predominance of the typhoid, in others a predominance of the malarial manifestations, and in others a combination of both of these elements, and in some of these last cases an apparent clinical fusion of the two elements.[20,24,33] The view is also held by some that the malarial manifestations remain latent during the course of the typhoid.[43] As a rule, the Italian observers[23,30,36] state that the two diseases are coincident and superimposed, each preserving its individuality.

---

* Several American writers of note state that the course of the disease is not less severe than that of simple typhoid fever, but the vast majority of American physicians, especially in the South, who describe "typho-malarial" fever, hold the view that the disease is much milder and less dangerous than typhoid fever. The following example is fairly illustrative: At a summer hotel an epidemic of typhoid fever occurred due to contaminated well water, and a large number of people were simultaneously taken with the disease. In one family three cases occurred, of which one, with a severe attack, was diagnosticated as typhoid fever, and the other two, with mild attacks, as "typho-malarial" fever.

It is thus seen that the usual American descriptions of "typho-malarial fever" differ essentially from the French, and we shall now consider which view, if either, is sustained by the evidence of our thirty cases of true combined typhoid and malarial infection.

A glance at these cases shows that, as a rule, the course of the disease was of at least average severity as compared with typhoid fever and generally of greatly increased severity. Only one or two cases exhibited a mild course. The mortality was high. Ten of the thirty cases ended fatally, a mortality of 33.3 per cent. This high rate of mortality is nearly double that of typhoid fever, if we take a large body of typhoid statistics covering a long period of years and collected from different climates and regions of the world. Complications, often severe, are seen to have occurred in a large number of the cases. Rose-spots are specifically mentioned in twenty of the cases, and in several of the other cases they may have occurred, although the notes are silent on this point. Quinine was given on the appearance of malarial manifestations in nearly all, if not, in fact, in all of the cases, and is seen to have had an unfailing influence, either controlling the malarial element for a period or removing it entirely from the scene. Quinine thus shows itself to be a true remedial agent, and appears to be as efficacious in controlling the malarial element in the combined infection as it is in uncomplicated cases of malarial fever. It is also of diagnostic value,[41,43] second only in importance to the microscopical examination of the blood.

As to the clinical picture presented in our cases, no uniformity is found. The typhoid picture, however, was always present, and in nearly all of the cases dominated the scene. The malarial manifestations appeared at different points in the different cases. Repeated paroxysms of chill, fever, and sweating at the onset of the disease appeared in many of the cases, in this respect resembling the picture generally described in "typho-malarial" fever. In other cases these features were absent. In some of the cases febrile paroxysms occurred during the height of the disease and irregularly through its course, though this was the exception. In other cases the malarial paroxysms occurred only in the convalescence from the typhoid. It is interesting to note also that in several cases malarial paroxysms directly preceded or accompanied the onset of the typhoid, disappeared completely from view during its course and again reappeared during convalescence. This would seem to indicate, as Baccelli,[30] Laveran,[43] and others[36] have suggested, that the typhoid fever is the more masterful disease, and to illustrate the truth of the old adage, "de duobus morbis corpus unum obsidentibus potior alterum obscurat;" but the important fact must not be forgotten in this connection that quinine was freely used against the malarial element whenever it appeared, and in all probability completely changed the clinical picture that would otherwise have been seen, and I am firmly convinced that had the malarial involvement been left untreated to pursue its own course the composite clinical picture would have been very different from what it actually was after quinine had removed the malarial participation in the course of the disease. There appears to be every reason for believing that without the interference of quinine the malarial paroxysms of chill, fever, and sweating would have continued to complicate the picture of the typhoid and would have caused an appearance of a thorough mixture and fusion of the malarial and typhoidal elements of the disease, as has been claimed by many American writers. The malarial element in our cases seems to have been suppressed from view by the quinine, but in many cases reappeared at one point or another whenever, in the struggle for existence, its power became strong enough to assert itself visibly.

Before dismissing the subject of paroxysms of chill, fever, and sweating, described as occurring so commonly at the onset of "typho-malarial" fever, it is well to remember that similar paroxysms are sometimes seen at the onset of simple typhoid, and even at times during its course, as Osler[32] has well shown. Profuse and repeated sweating is sometimes, though rarely, seen in typhoid fever of so pronounced a character as to have given rise to the term "sudoral typhoid" of Italian and French writers. Jaundice is another rare complication of typhoid fever, being seen in only 1.1 per cent. of the Munich[22] autopsies.

A few other clinical features of our cases remain to be pointed out. Abdominal symptoms in most of the cases were marked, not slight, as the American writers describe in "typho-malarial" fever. Bilious symptoms in these cases were not more prominent than would be expected in such a series.

If we add to our thirty cases of true combined typhoid and malarial infection many other cases described in the literature[18 19 20 24] that do not meet the criteria we have established for admitting them to our enumeration, but, nevertheless, resting upon sufficiently detailed clinical observations to establish as very probable their authenticity, we shall find in them strong confirmation of almost all of the facts observed in our thirty cases, although, of course, individual differences occasionally occur. Most of these cases are recorded in the French literature, though some few described by American writers are also found.

What, then, is the result of our study bearing on the question of the prevalence of a "typho-malarial" fever? It is seen that our cases of true combined typhoid and malarial infection offer little or no support for the "typho-malarial" fever as described clinically by American physicians, but, on the contrary, support strongly the observations of the French writers who have described a "typho-malarial" fever. It is seen that the "typho-malarial" fever of the French observers is a true combined typhoid and malarial infection; but the "typho-malarial" fever described as so prevalent in the United States, and especially in the Southern States, is not, as a rule, certainly a true combination of typhoid and malarial disease. The important point of difference clinically between the "typho-malarial" fever of American and French writers is found in the *severity and mortality* of the disease. The statistics of the United States army[14] during the war show the mortality from "typho-malarial" fever to have been less than one-third of the mortality due to simple typhoid fever. Such figures, of course, show that the "typho-malarial" fever reported during the war was not true combined typhoid and malarial fever, but doubtless it was either very mild simple typhoid (generally) or continued malarial fever.

Unfortunately, very few observers of the "typho-malarial" fever of our Southern States have studied their cases with modern methods of scientific investigation. However a few scientific observations on the subject have been recorded.[27] [28] [29] [37] [40] [41] Dock,[27] of Galveston, Texas, stated, in 1894, that in his wide experience he had never encountered a case of combined typhoid and malarial fever, nor had he ever seen the Southern type of "typho-malarial" fever. He had "offered to go anywhere where a doctor had a case of continued malarial fever or typho-malarial fever," in order to discover the malarial parasite in the blood of a typhoid case, but he had never found such a coincidence. He conducted six autopsies on cases diagnosticated by experienced men as "typho-malarial," and in all cases found simple typhoid fever. At the Johns Hopkins Hospital in Baltimore, where hundreds of cases of typhoid fever and of malarial fever are seen, many coming from the neighboring Chesapeake Bay region and from the Southern States, the "typho-malarial" fever of Southern writers is unknown, and only two cases of true combined typhoid and malarial infection have been seen. The reports from foreign countries in general are the same. The Italian observers,[23] [30] so fortunately placed to study this subject, are not acquainted with the American type of "typho-malarial" fever. Rho[36] states that not a single such case has been reported from Italy. It therefore seems clear that the disease described as so prevalent in our Southern States is not a true combination of typhoid and malarial fever. It seems probable that future investigations will show it to be most often a mild form of simple typhoid fever,[27,31,37] and in some cases irregular continued malarial fever.

That continued malarial fever often shows a picture so close to that of typhoid fever that a diagnosis is very difficult is well known, and such cases are not infrequently seen in the Johns Hopkins Hospital, and have been described by all writers on malarial fever.[30,39,41,42,43] Exact observations must be made in the Southern States, and the microscopical and clinical laboratory methods of study must be employed more generally before the exact truth about the "typho-malarial" fever can be known.

It is especially to be desired that systematic observations on this subject may be made by our army surgeons situated at various places in the Southern States.

In regard to the relative frequency of occurrence of true combined typhoid and malarial infection, what are we to infer from our study? Do we agree with the conclusions of Rho,[36] writing in Italy, who says: "The term typho-malarial fever has caused much uncertainty in medicine and much error of diagnosis; so far as relates to the contemporaneous infection of malaria and typhoid, the matter reduces itself to a rare coincidence, to a simple complication, which does not merit a special name."

I think that our statistics show evidence that, on the whole, this conclusion is rather too sweeping, but would apply with a considerable degree of accuracy to temperate climates where malarial fever is not common. In southern and tropical countries, where malarial fever is endemic and typhoid fever prevalent, it seems entirely probable that cases of combined infection are fairly common. This view is supported by Vincent's seventeen cases from Madagascar and Algeria, Laveran's two cases from Algeria, Kinyoun's five cases, coming from our Southern States, and by many other observations made in southern countries, and especially by French physicians in the countries lying in the Mediterranean basin. The mere mathematical theory of chance would also support this view.

It is probable that cases of true combined malarial and typhoid infection are not uncommon in our Southern States, but such cases are certainly not the cases that have been described from the South under the name "typho-malarial" fever. It is to be sincerely regretted that this misnomer has become so general, involving as it does an error of diagnosis and sometimes useless and even vicious therapeutic measures.

There is no excuse for preserving the term, and we may hope that the near future will find it thoroughly eliminated from use.

BIBLIOGRAPHY.

1. Burserius. Instit. Med., Milan, 1781, vol. i.

2. Hermann Schmidt. Uber des Europæische Sommerfieber, Paderborn und Armsberg, 1830.

3. Maillot. Traité des fièvres intermittentes, 1836.

4. Félix Jacquot. Lettres d'Italie, Gaz. méd. de Paris, 1851.

5. Daniel Drake. The Principal Diseases of the Interior Valley of North America. Second series, Philadelphia, 1854.

6. S. H. Dickson. Elements of Medicine, Philadelphia, 1855.

7. Circular No. 15, Surgeon-General's Office, Washington, September 8, 1863.

8. Woodward. Outlines of the Chief Camp Diseases of the United States Armies, as Observed During the Present War. Philadelphia, 1863.

9. Levick. Miasmatic Typhoid Fever. THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, April, 1864.

10. Circular No. 6, Surgeon-General's Office, Washington, November 1, 1865.

11. Wood. Treatise on the Practice of Medicine. Sixth edition. Philadelphia, 1866.

12. Bartholow. Camp Fevers. Memoirs of the United States Sanitary Commission, Medical volume. New York, 1867. Chap. II.

13. Frison. Rec. mém. de méd. milit., 1867.

14. The Medical and Surgical History of the War of the Rebellion, 1861-65. Washington, 1870, part i. vol. i.

15. Virchow. Kriegstyphus und Ruhr. Virchow's Archiv, 1871, Bd. lii. S. 1, pp. 5 and 30.

16. Cochran. Typho-malarial Fever. Trans. Med. Assoc. State of Alabama, 28th Session, 1875. Montgomery, Ala., 1875. Note B 1.

17. Woodward. Typho-malarial Fever: Is it a Special Type of Fever? Trans. International Med. Congress of Philadelphia. Philadelphia, 1876.

18. Laveran. Traité des fièvres palustres, Paris, 1884.

19. Cohn. De la marche de la fièvre typhoide chez les paludéens. Thesis, Paris, 1888.

20. Kelsch and Kierner. Traité des Maladies des Pays Chauds, Paris, 1889.

21. Kinyoun. Entero-malarial Fever. Abstract of Sanitary Reports, Marine Hospital Bureau, Washington, 1890, vol. v.

22. Münchener medicinische Wochenschrift, 1891.

23. Ascoli. Sull' utilitá dell' esame del sangue nella diagnosi di malaria. Bull. Soc. Lancisiana, Rome, April 11, 1891.

24. Gancel. Étude sur la fièvre typho-palustre. Arch. Méd. et Pharmac. milit., Paris, 1892, vol. xx.

25. Young. Typho-malarial Fever, so-called. Med. and Surg. Reporter, Philadelphia, 1892, vol. lxvii.

26. Thompson. Notes on the Observations of Malarial Organisms in Connection with Enteric Fever. Trans. Assoc. Amer. Phys., 1894, vol. ix.

27. Dock. Discussion of Thompson's (see 26) paper, Trans. Assoc. Amer. Phys., 1894, vol. ix. p. 126.

28. Osler. Report on Typhoid. The Johns Hopkins Hospital Reports, Baltimore, 1895, vol. iv. p. 61.

29. Thayer and Hewetson. The Malarial Fevers of Baltimore. The Johns Hopkins Hospital Reports, Baltimore, 1895, vol. v. p. 76.

30. Baccelli. Studien über Malaria (German edit.), Berlin, 1895.

31. Osler. Practice of Medicine, 1895, New York, second edition.

32. Osler. Chills in Typhoid Fever. University Med. Mag., November, 1895.

33. Vincent. Sur la symptomatologie et la nature de la fièvre typho-palustre. Le Mèrcredi Médical, December 4, 1895, vol. vi.

34. Colin. Presentation of Vincent's paper (33) to the Academy of Medicine, with remarks. Bull. Acad. de Méd., October 29, 1895, third series, vol. xxxiv.

35. Anders. A Statistical Study of the Complications of Malaria. Journ. Amer. Med. Assoc., Chicago, 1895, vol. xxiv.

36. Rho. La Malaria. Torino, 1896.

37. Gordon. Typho-malarial Fever: What is It? (and discussion). Virg. Med. Semi-monthly, Richmond, 1896-97, vol. i.

38. Da Costa. The Coexistence of Typhoid and Malarial Infection. International Clinics, Philadelphia, 1897, seventh series, vol. i.